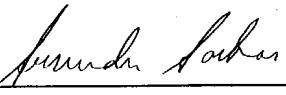


FORM PTO-1390 (Modified) (REV 1-2000)		U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE		ATTORNEY'S DOCKET NUMBER
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371				218090US6PCT
INTERNATIONAL APPLICATION NO. PCT/EP00/06355		INTERNATIONAL FILING DATE 5 July 2000		U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR 10/030697
TITLE OF INVENTION BIOREACTOR				PRIORITY DATE CLAIMED 12 July 1999
APPLICANT(S) FOR DO/EO/US WECHSLER Thomas et al.				
Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:				
<ol style="list-style-type: none"> <input checked="" type="checkbox"/> This is a FIRST submission of items concerning a filing under 35 U.S.C. 371. <input type="checkbox"/> This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371. <input checked="" type="checkbox"/> This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (24) indicated below. <input checked="" type="checkbox"/> The US has been elected by the expiration of 19 months from the priority date (Article 31). <input checked="" type="checkbox"/> A copy of the International Application as filed (35 U.S.C. 371 (c) (2)) <ol style="list-style-type: none"> <input type="checkbox"/> is attached hereto (required only if not communicated by the International Bureau). <input checked="" type="checkbox"/> has been communicated by the International Bureau. <input type="checkbox"/> is not required, as the application was filed in the United States Receiving Office (RO/US). <input checked="" type="checkbox"/> An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)). <ol style="list-style-type: none"> <input checked="" type="checkbox"/> is attached hereto. <input type="checkbox"/> has been previously submitted under 35 U.S.C. 154(d)(4). <input checked="" type="checkbox"/> Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3)) <ol style="list-style-type: none"> <input type="checkbox"/> are attached hereto (required only if not communicated by the International Bureau). <input type="checkbox"/> have been communicated by the International Bureau. <input type="checkbox"/> have not been made; however, the time limit for making such amendments has NOT expired. <input checked="" type="checkbox"/> have not been made and will not be made. <input type="checkbox"/> An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)). <input type="checkbox"/> An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)). <input type="checkbox"/> An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)). <input type="checkbox"/> A copy of the International Preliminary Examination Report (PCT/IPEA/409). <input checked="" type="checkbox"/> A copy of the International Search Report (PCT/ISA/210). 				
Items 13 to 20 below concern document(s) or information included:				
<ol style="list-style-type: none"> <input checked="" type="checkbox"/> An Information Disclosure Statement under 37 CFR 1.97 and 1.98. <input type="checkbox"/> An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included. <input type="checkbox"/> A FIRST preliminary amendment. <input type="checkbox"/> A SECOND or SUBSEQUENT preliminary amendment. <input type="checkbox"/> A substitute specification. <input type="checkbox"/> A change of power of attorney and/or address letter. <input type="checkbox"/> A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825. <input type="checkbox"/> A second copy of the published international application under 35 U.S.C. 154(d)(4). <input type="checkbox"/> A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4). <input type="checkbox"/> Certificate of Mailing by Express Mail <input checked="" type="checkbox"/> Other items or information: 				
Notice of Priority/Form PTO-1449 Drawings (6 sheets)				

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR 107030697	INTERNATIONAL APPLICATION NO. PCT/EP00/06355	ATTORNEY'S DOCKET NUMBER 218090US6PCT																
24. The following fees are submitted:		CALCULATIONS PTO USE ONLY																
BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :																		
<input type="checkbox"/> Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO \$1040.00 <input checked="" type="checkbox"/> International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO \$890.00 <input type="checkbox"/> International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO \$740.00 <input type="checkbox"/> International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) \$710.00 <input type="checkbox"/> International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) \$100.00																		
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Surcharge of \$130.00 for furnishing the oath or declaration later than months from the earliest claimed priority date (37 CFR 1.492 (e)).		<input type="checkbox"/> 20 <input checked="" type="checkbox"/> 30 \$130.00																
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a. <input checked="" type="checkbox"/> A check in the amount of \$1,020.00 to cover the above fees is enclosed. b. <input type="checkbox"/> Please charge my Deposit Account No. _____ in the amount of _____ to cover the above fees. A duplicate copy of this sheet is enclosed. c. <input checked="" type="checkbox"/> The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 15-0030 A duplicate copy of this sheet is enclosed. d. <input type="checkbox"/> Fees are to be charged to a credit card. WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.																		
NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.																		
SEND ALL CORRESPONDENCE TO: <div style="border: 1px solid black; padding: 10px; text-align: center;"> Surinder Sachar Registration No. 34,423  22850 </div>																		
<div style="text-align: right; margin-bottom: 10px;">  SIGNATURE </div> <div style="text-align: right;"> Gregory J. Maier NAME 25,599 REGISTRATION NUMBER Jan 14 2002 DATE </div>																		

218090US-6 PCT

REC'D PCT/PTO 10 APR 2002

#5

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF

THOMAS WECHSLER ET AL. : ATTN: APPLICATION DIVISION

SERIAL NO: 10/030,697 :

FILED: 14 January 2002 :

FOR: BIOREACTOR :

PRELIMINARY AMENDMENT

ASSISTANT COMMISSIONER FOR PATENTS
WASHINGTON, D.C. 20231

SIR:

Prior to a first examination on the merits, please amend the above-identified application as follows:

IN THE CLAIMS

Please cancel Claims 1-16 without prejudice.

Please add new Claims 17-32 as follows:

17. (New) Bioreactor for cultivating organic material by a nutrient medium, which can be put into a flow, comprising:

a housing;

a receiving device arranged in the housing, which has a receiving space for the organic material that can be flowed through by the nutrient medium;

at least two partition wall elements, which enclose the receiving space and each

- having a membrane, which is permeable to the nutrient medium and are substantially impermeable to the organic material; and

a carrier element, arranged in the receiving space, which is permeable to the nutrient medium and is configured as a fabric for an adhesion of the organic material;

wherein

the housing is constructed as a flat cell having annular carrier plates,

the partition wall elements have a supporting fabric, to which the membrane is applied, and

both the supporting fabric with the applied membrane and the fabric of the carrier element are each mounted in an annular carrier plate,

18. (New) Bioreactor according to claim 17, wherein the carrier element has a three-dimensional structure.

19. (New) Bioreactor according to claim 17, wherein the carrier element includes a textile carrier material.

20. (New) Bioreactor according to claim 19, wherein the textile carrier material is surface-treated, and a bio-compatible surface is formed with a structure adapted for an adhesion of the organic material.

21. (New) Bioreactor according to claim 17, wherein a receiving device of the flat cell is designed circularly.

22. (New) Bioreactor according to claim 17, wherein a number of flat cells are arranged as modules in one flow direction in at least one of a parallel and serial fashion.

23. (New) Bioreactor according to claim 17, further comprising:

a control device by which at least one of a flow generating device, a temperature adjusting unit, a gasing unit, a degasing unit, and further supply units can be controlled.

24. (New) Bioreactor according to claim 23, further comprising:

a sensor device arranged in one flow direction after the receiving space, by which physical and chemical values of a state of the nutrient medium can be determined; and the sensor device is connected to the control device.

25. (New) Bioreactor according to claim 17, further comprising:

a closed housing in which the receiving device is arranged; and at least one feed and one discharge are provided for the nutrient medium as well as an access for introducing and removing the organic material.

26. (New) Method for cultivating organic material, wherein

a nutrient medium is at least temporarily put into a flow,

the organic material is introduced into a receiving device of a bioreactor,

the nutrient medium is passed through the receiving device of the bioreactor for a convective supply of the organic material, and

a bioreactor according to claim 17 is used.

27. (New) Method according to claim 26, wherein prior to an inoculation or introduction of the organic material into the receiving device this is sterilized.

28. (New) Method according to claim 26, wherein prior to a removal of the cultivated organic material from the receiving device a medium, in particular an enzyme, is introduced for detaching adhered organic material.

29. (New) Method according to claim 26, wherein the direction of flow of the nutrient medium that is passed through the receiving device is changed during cultivation of the organic material.

30. (New) Method according to claims 26, wherein at least one of a chemical and physical state of the nutrient medium, a stoichiometrical composition, temperature, pressure or rate of flow, are specifically changed during the cultivation.

31. (New) Method according to claim 26, wherein at least after passing the nutrient medium through the receiving device at least one of chemical and physical values of state of the nutrient medium are measured, the measured values of state are recorded and analyzed in a control device, and the measured values of state are employed for controlling the cultivation of the organic material.

32. (New) Method according to claim 26, wherein the nutrient medium is passed through a number of receiving devices, which are arranged to each other in at least one of a parallel and serial fashion.

IN THE ABSTRACT

Please cancel the original Abstract on page 27 in its entirety and insert therefor:

ABSTRACT

A bioreactor as well as a method for cultivating organic material, in particular cells, by a nutrient medium. For an intensive cultivation of the organic material in a simple and reliable handling a flow generating device is provided in the bioreactor, by which the nutrient medium can be put into a flow. A receiving device is arranged in the flow that is adapted for receiving and/or retaining the organic material, and the receiving device is adapted for passing through the flowing nutrient medium is permeable. In the method the nutrient medium is at least temporarily put into a flow, the organic material, in particular cells, is

retained in or at a receiving device, which is permeable to the nutrient medium, and the nutrient medium is passed through the receiving device.

REMARKS

Favorable consideration of this application, as presently amended, is respectfully requested.

The present Preliminary Amendment is submitted to place the above-identified application in more proper format under United States practice.

By the present Preliminary Amendment claims 1-16 are cancelled and new claims 17-32 are presented for examination. New claims 17-32 are deemed to be self-evident from the original disclosure, including claims 1-16, and thus are not deemed to raise any issues of new matter. No differences between new claims 17-32 and cancelled claims 1-16 are believed to narrow the scope of claims 17-32 in any aspect.

A new Abstract believed to be in more proper under United States practice is also submitted herein.

The present application is believed to be in condition for a full and thorough examination on the merits. An early and favorable consideration of the present application is hereby respectfully requested.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.



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218090US-6 PCT

Marked-Up Copy
Serial No:
10/030,697
Amendment Filed on:
4-10-2002

IN THE CLAIMS

Claims 1-16 (Cancelled).

Claims 17-32 (New).

IN THE ABSTRACT

Abstract (New).

6/PW

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S 746

Bioreactor

The invention relates to a bioreactor as well as a method for cultivating organic material according to the generic part of claims 1 and 15, respectively.

The cultivation of organic material, in particular of human or animal cells, increasingly gains in importance in medical diagnostics, therapy and pharmacology.

Of particular interest in this is the multiplication of hematopoietic parent cells. These are taken from a patient before a radiotherapy or chemotherapy and are to be retransplanted into the patient in a greatest number possible after the conclusion of the radiotherapy or chemotherapy.

In this method, among others, cryoconservation is commonly used, in which withdrawn blood parent cells are frozen for the duration of the radiotherapy or chemotherapy. However, an enrichment of the cells is not possible with this. On the contrary, the number of living cells and their vitality is drastically reduced.

Methods for cultivating and enriching different cells of human origin have already been developed and established.

Typically, cells are cultivated in containers or Petri dishes, in which a nutrient medium is located that is suitable for the cultivation of the respective cell type. In general, several treatment steps are required during the cultivation, such as the exchange of the nutrient medium as well as a displacement of cultivated cells into other containers.

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Due to the repeatedly required interference in the cultivation process there is a growing risk of contaminating the cell material, for example through laboratory equipment or the ambient atmosphere, as a result of which the material to be cultivated becomes useless for the further utilization.

In all, the handling of the entire cultivation process entails relatively great expense so that a clinical utilization on a large scale is hardly practicable.

Furthermore, a cultivation of cells in hollow fibres was tested. Here the cells located in the hollow fibres are diffusively supplied with nutrients from the fibre periphery. At the beginning of the cell cultivation relatively good growth rates can be achieved with this, but with an increasing number of cells present in the spatially limited hollow fibres a further multiplication becomes problematic.

A similar problem exists in the preamble-forming bioreactor and the preamble-forming method according to EP 0 121 981 A1. A porous, monolithic ceramic block, which is interspersed with a number of fine channels that extend in parallel, is inoculated with cells. The cells add to the porous inside of the channels, which are flowed through by a nutrient solution.

The invention is based on the object to develop a device and a method for cultivating organic material, which allow an intensive cultivation of an organic material on the one hand and can be handled in a particularly easy and reliable manner on the other hand.

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The object is solved in accordance with the invention by the bioreactor having the features of claim 1 and by the method according to claim 15.

In the bioreactor it is intended that a flow generating device is provided, by means of which the nutrient medium can be put into a flow, that a receiving device is arranged in the flow, which is adapted for receiving and/or retaining the organic material, and that the receiving device is permeable for passing through the flowing nutrient medium.

A basic idea of the invention resides in the convective supply of the organic material with nutrient medium. This supply can take place in a continuous or quasi-continuous manner. By this it is possible to ensure an almost optimum provision of the required nutrients over the entire duration of the cultivation, while metabolic products, which are detrimental to cell growth, are at the same time quickly removed by the flow of the nutrient medium. Tests carried out with hematopoietic parent cells have shown excellent growth and vitality rates.

The bioreactor includes a closed housing having at least one feed and one discharge and at least a flow channel, and here a gradient or commonly used pump devices, such as hose pumps, can be employed to generate the flow.

In principle, other devices that are capable of putting the nutrient medium into flow are also suitable. The rate of flow and the quantity of flow are adjusted in such a way that the organic material remains largely immobilized in the receiving device. The nutrient medium flows transversely through the receiving device from one partition wall element to the other, with the organic material being arranged in a substantially transverse manner to the flow.

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With the bioreactor according to the invention an uninterrupted supply of the organic material with the necessary nutrient media and substances is rendered possible through a feeding taking place during the entire cultivation process, as a result of which the handling and performance of the cultivation process is simplified to a considerable degree. Due to the omission of a repeated external interference in the cultivation process and of the greater risk of contamination related therewith the reactor according to the invention is also particularly suited for the large-scale clinical use.

The constantly good supply of the organic material with nutrients allows an intensive cultivation of the material, whereby enrichment values of the cells can reach the factor 10 and above. By comparison, in the cultivation of cells in cultivating containers or Petri dishes enrichment factors are typically achieved that merely range between 2 and 4 despite a considerably greater expense.

In general, the bioreactor in accordance with the invention is suited for cultivating various kinds of organic material. Concerned here are preferably simple structures, such as bacteria, viruses, fungi or body cells. Apart from the parent cells these are, among others, microvascular and macrovascular endothelial cells from the spleen, the suprarenal gland and the aorta, different cell types from the cornea, cells of the eye lens and the retina, cells from the skin, bones as well as the bone marrow. In principle, the cultivation of more complex structures, for instance of entire organs or parts thereof, is also possible.

The bioreactor in accordance with the invention is characterized in that the receiving device has at least two

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partition wall elements, by which a receiving space is enclosed, that the organic material is arranged in the receiving space and that the partition wall elements are on the one hand permeable to the nutrient medium and on the other hand substantially impermeable to the organic material. Due to the impermeability of the partition wall elements to the organic material a defined immobilization of the organic material in the receiving device is achieved on the one hand. A washing away of the organic material is prevented, as this is enclosed in a defined space in the flow. In this defined space, which preferably extends over the entire flow cross section and has a relatively small design, the organic material can also move to a certain extent, which leads to a uniformly good settlement with cells. On the other hand, owing to the permeability of the partition wall elements to the nutrient medium a continued good convective supply of the organic material and consequently an intensive cultivation of the same is ensured.

In principle, different kinds of material are possible for being used in the partition wall elements, which have the required permeability for a medium to be fed. They can consist e.g. of fabrics, wefts or felts or of other permeable materials. Fabrics have proved to be particularly useful for bioreactors employed for cultivating liver cells. With their relatively coarse meshes fabrics generate an excellent diffusion effect in the flowing nutrient medium.

However, it is particularly preferred if the partition wall elements have a membrane. Since membranes can be produced with differing properties regarding their permeability as well as their selective behaviour, the supply of the cells that are to be cultivated in the bioreactor with particular substances can be specifically influenced by using a suitable membrane. Moreover, by choosing membranes, which are

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reinforced in different manners, the mechanical stability of the partition wall elements can likewise be specifically adjusted and adapted to the respective requirements of the organic material, e.g. in the case of adherent cells. As reinforcement of the membrane for instance textile reinforcements, such as fabrics or wefts, can be used. The use of organic or anorganic membranes, for example of a polymer, metal or ceramics or of a combination of these materials, is possible.

In order to obtain a particularly good immobilization of the organic material provision is made in the bioreactor according to the invention for the receiving device to include a carrier element, which is adapted for adding the organic material and is permeable to the nutrient medium. An addition of the organic material to the substantially plane carrier element can be achieved by a specific structure of the carrier element and/or by the flow pressure. The carrier element can constitute the receiving device by itself or preferably in combination with the partition wall elements. This embodiment is suited, among others, for the cultivation of implants, for instance of in-vitro cultivated skin areas, for which a large-surface arrangement of the immobilized cells is required.

In this it is of advantage if the carrier element includes a textile carrier material. Through the appropriate choice e.g. of the fabric type and material, the filament strength, the mesh width and the number of threads an almost ideal relation between surface and reactor volume as well as good flow properties for the nutrient supply of the cells can be adjusted in a simple way for each case of application. This allows a specific influencing and promotion of the cultivation of the organic material.

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As textile carrier materials technical fabrics, wefts and folds are suitable, in which the structure of monofilaments or wires is exactly defined. The monofilaments or wires may consist for example of metal, ceramics, synthetic and/or natural materials, such as cellulose, with or without surface coatings. In particular cases multifilament fabrics are also useful, in which the threads that define the fabric structure consist for their part of a number of smaller threads.

A specific incorporation of cells in the carrier element can be achieved by a three-dimensional structure. The carrier element can be for instance a porous plastic or ceramic material or a so-called three-dimensional technical fabric. Fabrics of this type have two or more superposed and partly connected or woven fabric matrices that offer a secure support for incorporated cell material. Furthermore, a three-dimensional structure can be obtained by folding, pleating or rolling an approximately two-dimensional element. In addition, a skeleton structure of the carrier element or an arrangement of structural elements, as for example tube members or honeycombs, can be provided. Finally, so-called non-woven materials and bonded fabrics can also be applied.

When using technical fabrics as carrier element it is of advantage if the technical fabric is surface-treated and a bio-compatible surface with a structure adapted for an adhesion of the organic material is formed. In this way the surface of a stable fabric, for example of polyester, polyamide, a trifluorethylene/ethylene copolymer, metal or ceramics, can be specifically functionalized for different purposes. For instance cell growth can be positively influenced by generating a hydrophilic fabric surface or by increasing the concentration of nitrogenous functional groups. By comparison, other substances, such as e.g.

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immunoglobulin G (IgG), are preferably adsorbed at hydrophobic surfaces.

A particularly effective surface treatment are low temperature plasma methods, by means of which for example textile materials of polymer, metal or ceramics and membranes can be specifically coated with an inert surface and thus be functionalized without having to expose the fabric to be treated to aggressive solutions or high temperatures. In this way different material properties, such as e.g. a high mechanical stability of a basic carrier material, can be systematically combined with desired surface properties, such as e.g. hydrophilicity and cell adhesion.

It is intended that the bioreactor according to the invention is constructed as a flat cell, in which the receiving device preferably has a circular design. In a circularly designed hollow space in the flat cell a particularly good flow and consequently a constant supply of the cells to be cultivated with nutrient medium is ensured. The flat cell can be designed in layers, for instance of glued plastic elements, which results in a bioreactor that is compact and at the same time simple to produce. The simple producibility even allows the employment of the bioreactor as a single-use article, which may be of advantage for medical applications. At the same time the flat cell is of such robustness that a sterilisation carried out by means of autoclaving or γ -sterilisation is possible. For the inoculation and reaping of larger organic material, as for example of implants, the bioreactor can be mounted or dismounted.

An alternative embodiment of the invention resides in the fact that the bioreactor is constructed as a tube cell, in which the partition wall elements have a tubular design. Such

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a tubular arrangement of the partition wall elements leads to a particularly compact embodiment.

A particularly good flow of the nutrient medium is achieved according to the invention in that the tubular partition wall elements are arranged paraxially, preferably coaxially to each other. In the coaxial arrangement, in which the carrier element can also be designed cylindrically and arranged between the two tubular partition wall elements, a flow of the nutrient medium occurs radially from the outside to the inside or radially from the inside to the outside. A dependable positioning of the individual elements to each other is ensured by radially extending crosspieces or support members that are attached to the surrounding housing. An especially uniform feeding and discharge of the nutrient medium is achieved in that inside the outer tubular partition wall element a number of internal, tubular partition wall elements are arranged, which extend paraxially to each other.

In another embodiment of the invention it is of advantage if a number of flat cells or tube cells are arranged as modules in one flow direction in a parallel and/or serial fashion. In this the medium flowing from a first flat cell can be directly fed to further flat cells such that a particularly effective use of the nutrient medium and a possible utilization of metabolic products of a previous cell is rendered possible. As a rule, however, a parallel arrangement is useful in order to exclude any contamination caused by metabolic products.

In a preferred embodiment of the bioreactor a control device is provided, by means of which the flow generating device, a temperature adjusting unit, a gasing unit and/or further supply units can be controlled and/or regulated. Through this it is possible to specifically influence the cultivation

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process of the organic material through various parameters, such as the rate of flow, the quantity of flow, the temperature and pressure of the nutrient medium as well as the feeding and discharge of further media and substances.

In particular, a control or a regulation of the different units by the control device is possible through a central predetermination of specific control or regulation programmes, which are brought into line with individual organic materials or cultivation processes according to requirement. Thus, an adjustment and control of different process parameters that is tailored to suit the requirements is rendered possible.

In this it is particularly advantageous if a sensor device is arranged in one flow direction after the receiving device, by means of which physical and chemical values of state of the nutrient medium can be determined and the sensor device is connected to the control device. With the sensor device e.g. the concentration of the nutrients or metabolic products present in the nutrient medium can be determined. Finally, due to the coupling of the sensor device to the control device a possibly required change of the chemical and physical values of state of the nutrient medium can be carried out. On account of the described coupling this change can be effected almost in „real time“, i.e. in a direct succession to the determination of the corresponding values of state.

Finally, in a preferred embodiment the bioreactor is characterized in that a closed housing is provided, in which the receiving device is arranged and at least one feed and one discharge are provided for the nutrient medium as well as an access for introducing and removing the organic material. Through the closed housing it is ensured that the inside,

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especially the receiving device of the bioreactor, still remains sterile after the production and sterilization of the bioreactor even after storage and transport. Moreover, a contamination-free cultivation of the organic material is rendered possible, since the individual treatment steps, e.g. the introduction and discharge of the organic material as well as the feeding and discharge of the nutrient medium or of other substances, can be performed with the housing being closed and thus the risk of a contamination of the organic material can be decreased considerably. Due to the simple construction of the bioreactor it can be produced at low cost and is particularly suited for being employed as a single-use article in the clinical field.

One aspect of the method in accordance with the invention and according to claim 15 resides in the fact that the nutrient medium, which is put into a flow, is passed through the receiving device retaining the organic material. Through this a cultivation of the organic material that is easy to handle and reliable is possible. In particular, by passing the nutrient medium through the receiving device, a good supply of the organic material retained thereon or therein with nutrients is ensured, as a continuous flowing round or, if required, infiltration with nutrient solution is achieved. The flow can be constant or pulsating.

In order to keep the risk of contamination for the organic material to be cultivated particularly small, it is of advantage if the receiving device is sterilized prior to inoculating or introducing the organic material into the former. The sterilization of the receiving device can be carried out e.g. on the part of the producer immediately after the production of the bioreactor. Through suitable measures taken to close the bioreactor the sterility of the receiving device can then be maintained until the time of

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application. However, it is also possible to carry out the sterilization of the receiving device only immediately before its application. In principle, both measures can be combined to ensure a particularly great freedom from contamination. Besides, a sterilization of the entire bioreactor is also possible, for example if especially high demands are made on securing sterility.

For a further simplification of the cultivation process it is intended that prior to the removal of the cultivated organic material a medium, in particular a physiological solution with an enzyme, such as a trypsin solution, is introduced for detaching and rinsing out the added organic material. Through this an interference in the closed bioreactor, as it is required for instance in the case of a mechanical detachment of the added organic material with suitable instruments, becomes unnecessary. Apart from this simplification of the handling the risk of both a contamination and a mechanical damage of the fabric can be greatly reduced as a result of this non-invasive detachment of the material. The rinsing solution can be fed through the same access as the inoculation with organic material. During the inoculation and the rinsing out, which is also referred to as reaping, it is useful to interrupt the nutrient medium flow.

A preferred embodiment of the method provides that the direction of flow of the nutrient medium, which is passed through the receiving device, is changed during the cultivation of the organic material. With this a good supply of the cells can be obtained especially in the case of organic material that has a great lateral extension and thickness. Any nutrient gradients that might appear in the material can be appreciably reduced in this way.

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To ensure a supply of the organic material with nutrients, which is adapted to the respective duration of the cultivation process, and to achieve thereby an intensive cultivation of the organic material provision is made in the method according to the invention that the material composition, the stoichiometrical composition, the state or rate of flow of the nutrient medium are changed during the cultivation.

Moreover, it is of advantage in this if chemical and/or physical values of state of the nutrient medium are measured when the nutrient medium is passed through the receiving device, that the measured values of state are analysed and the chemical and/or physical values of state of the nutrient medium are changed depending on the measured values of state. In this way chemical and/or physical parameters of the nutrient medium or of additional nutrients can be adapted particularly well to the changing requirements of the cells in the course of the cultivation process. In addition, especially metabolic products of the organic material can be determined through a lactate or CO₂ value present in the nutrient medium and can be employed very well for the control, monitoring and documentation of the cultivation process. This way the best moment for reaping can be determined, for example immediately before an undesired differentiation taking place during the cultivation of parent cells.

In the following a detailed description of the invention will be given with reference to drawings of preferred embodiments. In an extremely schematized representation

Fig. 1 shows a cross section of a preferred embodiment of the bioreactor according to the invention as flat cell;

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Fig. 2 shows a view onto an assembly of individual components of a bioreactor according to the invention;

Fig. 3 shows an assembled bioreactor as flat cell;

Fig. 4 shows a diagram of an installation with a bioreactor;

Fig. 5 shows a schematic view of another preferred embodiment of the bioreactor according to the invention as tube cell;

Fig. 6 shows a schematic cross-sectional view of the bioreactor according to Fig. 5;

Fig. 7 shows a cross-sectional view of a further embodiment of the bioreactor in accordance with the invention;

Fig. 8 shows a schematic cross-sectional view of an embodiment of the bioreactor according to the invention with a support frame;

Fig. 9 shows a longitudinal section through the bioreactor of Fig. 8; and

Figs. 10 to 14 show further cross-sectional views of alternative embodiments of the bioreactor in accordance with the invention.

The cross section shown in Fig. 1 of a preferred embodiment of a bioreactor 10 according to the invention for cultivating parent cells has a carrier element 12, partition wall

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elements 11, which are spaced therefrom and each consist of two parts, and a cover 14 located on both sides. Due to the distance pieces 16, which are provided between the individual elements and can be separate ring elements or part of the housing, an adjustment of a desired distance between the carrier element 12 and the partition wall element 11 or between the partition wall element 11 and the cover 14 is possible.

The covers 14 and the distance pieces 16 are produced of polycarbonate. The carrier element 12 is designed as a technical fabric. As fibre material preferably a monofilament consisting of polyamide 6.6 (PA 6.6) or polyethyleneterephthalate (PET) is used. The mesh width of the fabric amounts to an average of 20 μm and a thickness of approximately 55 to 60 μm . The weight of the fabric amounts to approximately 35 to 40 g/m^2 .

A receiving device for the organic material is constituted by the carrier element 12 and the partition wall elements 11, which laterally define a receiving space 13 of the receiving device. In the illustrated example the partition wall elements 11 each have a membrane, which is applied to a supporting fabric lying underneath. The membrane material includes polyamide 66 (PA 66). As supporting fabric for example monofilament fabrics made of polyethyleneterephthalate (PET) can be employed having a mesh width of approximately 265 μm , a thickness of around 200 μm and a typical weight of 85 g/m^2 . Typical membrane thicknesses range between 0.45 μm and 0.8 μm . For the spacing of the individual elements of the bioreactor the distance pieces 16 have a height of about 3 mm.

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Fig. 2 shows a view onto an assembly of individual components of the bioreactor 10 according to the invention. Between the two covers 14 there are several annular carrier plates 24, to which the carrier element 12 or the partition wall elements 11 are mounted that consist of a membrane 11a and a supporting fabric 11b. The circular forms of the employed fabrics or membranes are cut to a precise fitting, for example by means of a laser, with the carrier element 12 that is designed as technical fabric and the partition wall elements 11 being attached to the carrier plates 24 by means of an adhesive that is hardenable under ultraviolet light or welded thereto.

Together with the covers 14 the annular carrier plates 24 form a housing with a hollow space, into which lead lines for the feeding and/or discharge of fluids. In the present embodiment the feeding of the nutrient medium into the bioreactor 10 is effected via the feed line 19, while the discharge line 22 is provided for discharging the nutrient medium. The inoculation of the organic material as well as the feeding of a medium containing enzymes for detaching the added organic material is effected via two lines that lead into the receiving device of the bioreactor 10. For the ventilation of the bioreactor 10 a vent line 20 is arranged at the carrier plate 24 with the feed line 19.

As is shown in this embodiment, the carrier plates 24 that basically have the same construction take over the function of the distance pieces 16 depicted in Fig. 1. By variating the thickness of the individual carrier plates or of the distance pieces 16 the distance of the individual components of the bioreactor 10 can be excellently adapted to the conditions required for the cultivation of specific organic materials. An important role in this plays the relation of the reactor surface to the reactor volume, which can be

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adjusted by choosing the appropriate fabrics. Moreover, the distance between the individual components can also be slightly changed for example by inserting different sealings or intermediate plates, and here a dismounting is also possible by means of detachable mounting means.

Furthermore, the covers 14 can be followed by temperature cabinets (not depicted), which serve to maintain a constant process temperature during the cultivation of the organic material. Such temperature cabinets typically have an electric heating and/or cooling or are connected to a heating or cooling bath via feed and discharge lines. In principle, the storage of the bioreactor in a tempered warming cupboard is also possible.

The bioreactor 10 described in Fig. 2 with its individual components is shown in Fig. 3 as assembled, finished flat cell with feed and discharge lines. The bioreactor 10 in accordance with the invention has a compact format, which particularly simplifies its handling in the laboratory field as well as in the clinical field.

In connection with the diagram according to Fig. 4 a brief description is given of the most important steps in the operation of the bioreactor 10 that is employed for the cultivation of peripheral, hematopoietic parent cells. These parent cells are required for the transplantation of blood parent cells after a high dosage chemotherapy.

To inoculate the bioreactor 10 it is at first filled via a feed line 19 from a container 30 with nutrient medium, which flows radially into the hollow space of the reactor. The corresponding feed line 19 is at first closed by a stop valve 31, while a discharge line 22 remains open. The feed lines 21 provided for the inoculation are opened by means of their

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feed stop valves 32 and the parent cells, which were taken from a patient before the radiotherapy or chemotherapy, can be injected through these feed lines into the reactor module 10 for example by means of a syringe. After this process the feed lines 21 provided for the inoculation and the discharge line 22 are closed. The parent cells are located in the receiving device and can settle the latter.

After a certain time that is advantageous to an even distribution and settlement of the parent cells the feed line 19 and one discharge line 22 are opened to promote cell growth. Tempered nutrient solution is then fed through the feed line 19. In the course of the cultivation process the amount of nutrient solution fed per unit of time can be gradually increased, as there are more cells present with an increasing duration of the cultivation process so that the nutrient demand grows.

The feeding and discharge of the nutrient medium is effected in such a way that the hollow space of the bioreactor 10, which is circular in cross section, and consequently the receiving device is flowed through as uniformly as possible. Through this a same and constant nutrient gradient is ensured over the entire surface of the cell carrier. At the same time detrimental metabolic products are removed from the bioreactor 10 by the nutrient flow in a quick and reliable manner.

After the exit of the nutrient medium via the discharge line 22 the nutrient medium passes through a first measuring device 33, with which the content of nutrients and harmful substances as well as further physical and chemical values of state are determined. The determined values serve to control and monitor the cultivation process by means of an appropriate control device. This can furthermore be connected

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to a second measuring device 34 located in the feed line 19. After a cleaning and reprocessing carried out in a reprocessing unit 35 located in the circle the nutrient medium can be re-fed into the container 30, with a pump 36 being provided as flow generating device.

Finally, for the removal of cultivated cells enzymes are fed via the line 21, which cause a detachment of the parent cells from the carrier element 12. For this the discharge line 22 is closed through a stop valve 37 and a physiological solution is being fed. The parent cells can now be sucked off by means of a syringe through the line 21 provided for the inoculation. The parent cells produced thereby can now be washed and, if required, be submitted to further treatment steps before being used for a further application, e.g. as blood substitute or implant. For the ventilation a vent valve 38 is arranged at the module housing of the bioreactor 10.

In Fig. 5 another bioreactor 10a according to the invention is shown in perspective view as tube cell 7 having a tubular structure. The bioreactor 10a has a cylindrical outer wall 8a, within which concentrically arranged partition wall elements 11 or tubes are positioned. Between the two partition wall elements 11a a tubular carrier element 12a is arranged coaxially. In this bioreactor 10a in accordance with the invention the nutrient solution can flow axially along the tube, and here a pressure difference allows nutrient solution to flow radially from the outside to the inside or from the inside to the outside and thus transversely through the partition wall elements 11a and the carrier element 12a.

In Fig. 6 the coaxial arrangement of the individual tubular elements of the bioreactor 10a is depicted even more clearly, with an additional opening 17a being formed in the outer wall 8a. This opening 17a can be used for the feeding or discharge

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or for the introduction of a measuring probe. It can also serve to inoculate the culture.

Another bioreactor 10b according to the invention can be taken from Fig. 7, wherein two tube cells are provided in a tubular outer wall 8b. A single tube cell includes two tubular partition wall elements 11b, which are arranged coaxially to each other and between which a tubular carrier element 12b is inserted centrally.

From Figs. 8 and 9 a further bioreactor 10c according to the invention can be gathered. Just as in the embodiments described before a partition wall element 11c, a carrier element 12c and an internally disposed partition wall element 11c are provided coaxially to each other inside a cylindrical outer wall 8c. To stabilize the form the outer partition wall element 11c is mounted to an annular support member 15c, with several annular support members being axially connected to each other by means of embedded distance pieces 19c. On the radial inside of the annular support member 15c radial crosspieces 23 project inwards at an angular distance of 90° to each other, which end at the tubular carrier element 12c. Inside the tubular carrier element 12c a cross-shaped support element 21c is in turn provided with a central opening, in which the internal cylindrical partition wall element 11c is arranged coaxially.

A bioreactor 10d that is comparable to the bioreactor 10c described before is shown in Fig. 10. However, in the bioreactor 10d a total of three internal partition wall elements 11d is provided, which are arranged at an angular distance of 120° to each other inside the cylindrical carrier element 12d.

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In the tubularly constructed bioreactor 11e according to Fig. 11 the carrier element 12e is pleated, i.e. it is designed wavelike between the two partition wall elements 11e that are arranged coaxially to each other. Through this an especially large surface of the carrier element 12e is obtained.

In another bioreactor 10f according to Fig. 12, which is designed similarly to the bioreactor 10c according to Figs. 8 and 9, the carrier element 12f is arranged in a netlike or framewise manner between the two partition wall elements 11f that are held by a support member 15f.

Another bioreactor 10g, which is constructed in a comparable manner to the bioreactor 10d of Fig. 10, becomes apparent from Fig. 13. Here the carrier element 10g is likewise arranged in a netlike or framewise manner in the space between the two partition wall elements 10g.

Another bioreactor 10h in accordance with the invention is depicted in Fig. 14. A cylindrical outer wall 8h includes a support frame consisting of an annular support member 15h and an approximately clover-leaf shaped internal support member 21h held therein by means of four radial crosspieces 23h. On the outside of the annular support member 15h the external partition wall element 11h is mounted, whereas in the internal support member 21h a total of nine tubular partition wall elements 11h is disposed. To enlarge the surface of the carrier element 12h it is pleated, i.e. it is designed with a certain wave form.

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New Claim 1

1. Bioreactor for cultivating organic material, in particular cells, by means of a nutrient medium, which can be put into a flow, comprising
 - a housing,
 - a receiving device arranged therein, which has a receiving space (13) for the organic material that can be flowed through by the nutrient medium,
 - at least two partition wall elements (11), which enclose the receiving space (13) and each have a membrane (11a), which is on the one hand permeable to the nutrient medium and on the other hand substantially impermeable to the organic material, and
 - a carrier element (12) arranged in the receiving space (13), which is permeable to the nutrient medium and is designed as a fabric for an adhesion of the organic material,

characterized in that

- the housing is constructed as a flat cell having annular carrier plates (24),
- the partition wall elements (11) have a supporting fabric (11b), to which the membrane (11a) is applied and
- both the supporting fabric (11b) with the applied membrane (11a) and the fabric of the carrier element (12) are each mounted in an annular carrier plate (24).

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SEFAR AG

S 746

New Claims 2 to 16

2. Bioreactor according to claim 1,
c h a r a c t e r i z e d in that
the carrier element (12) has a three-dimensional
structure, in particular it is designed as three-
dimensional fabric.
3. Bioreactor according to claim 1 or 2,
c h a r a c t e r i z e d in that
the carrier element (12) includes a textile carrier
material.
4. Bioreactor according to claim 3,
c h a r a c t e r i z e d in that
- the textile carrier material is surface-treated and
- a bio-compatible surface is formed with a structure
adapted for an adhesion of the organic material.
5. Bioreactor according to any one of claims 1 to 4,
c h a r a c t e r i z e d in that
the receiving device of the flat cell (9) is designed
circularly.
6. Bioreactor according to any one of claims 1 to 5,
c h a r a c t e r i z e d in that
a number of flat cells (9) are arranged as modules in one
flow direction in a parallel and/or serial fashion.

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7. Bioreactor according to any one of claims 1 to 6,
c h a r a c t e r i z e d in that
a control device is provided, by means of which a flow
generating device, a temperature adjusting unit, a gasing
unit, a degasing unit and/or further supply units can be
controlled and/or regulated.
8. Bioreactor according to claim 7,
c h a r a c t e r i z e d in that
 - a sensor device is arranged in one flow direction after
the receiving space (13), by means of which physical
and chemical values of state of the nutrient medium can
be determined and
 - the sensor device is connected to the control device.
9. Bioreactor according to any one of claims 1 to 8,
c h a r a c t e r i z e d in that
 - a closed, in particular dismountable housing is
provided, in which the receiving device is arranged,
and
 - at least one feed and one discharge are provided for
the nutrient medium as well as an access for
introducing and removing the organic material.
10. Method for cultivating organic material, wherein
 - a nutrient medium is at least temporarily put into a
flow,
 - the organic material is introduced into a receiving
device of a bioreactor (11) and
 - the nutrient medium is passed through the receiving
device of the bioreactor (11) for a convective supply
of the organic material,c h a r a c t e r i z e d in that

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- a bioreactor (11) according to any one of claims 1 to 9 is used.
- 11. Method according to claim 10,
characterized in that prior to an inoculation or introduction of the organic material into the receiving device this is sterilized.
- 12. Method according to claim 10 or 11,
characterized in that prior to a removal of the cultivated organic material from the receiving device a medium, in particular an enzyme, is introduced for detaching adhered organic material.
- 13. Method according to any one of claims 10 to 12,
characterized in that the direction of flow of the nutrient medium that is passed through the receiving device is changed during the cultivation of the organic material.
- 14. Method according to any one of claims 10 to 13,
characterized in that a chemical and/or physical state of the nutrient medium, in particular a material composition, a stoichiometrical composition, temperature, pressure or rate of flow, are specifically changed in the course of the cultivation.
- 15. Method according to any one of claims 10 to 13,
characterized in that
 - at least after passing the nutrient medium through the receiving device chemical and/or physical values of state of the nutrient medium are measured,
 - the measured values of state are recorded and analysed in a control device, and

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- the measured values of state are employed for controlling and/or regulating the course of the cultivation of the organic material.

16. Method according to any one of claims 10 to 15 characterized in that

- the nutrient medium is passed through a number of receiving devices, which are arranged to each other in a parallel and/or serial fashion.

ABSTRACT

The invention relates to a bioreactor as well as a method for cultivating organic material, in particular cells, by means of a nutrient medium. For an intensive cultivation of the organic material in a simple and reliable handling a flow generating device is provided in the bioreactor according to the invention, by means of which the nutrient medium can be put into a flow, wherein a receiving device is arranged in the flow that is adapted for receiving and/or retaining the organic material and wherein the receiving device that is adapted for passing through the flowing nutrient medium is permeable.

The method in accordance with the invention is characterized in that the nutrient medium is at least temporarily put into a flow, that the organic material, in particular cells, is retained in or at a receiving device, which is permeable to the nutrient medium and that the nutrient medium is passed through the receiving device.

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FIG. 1

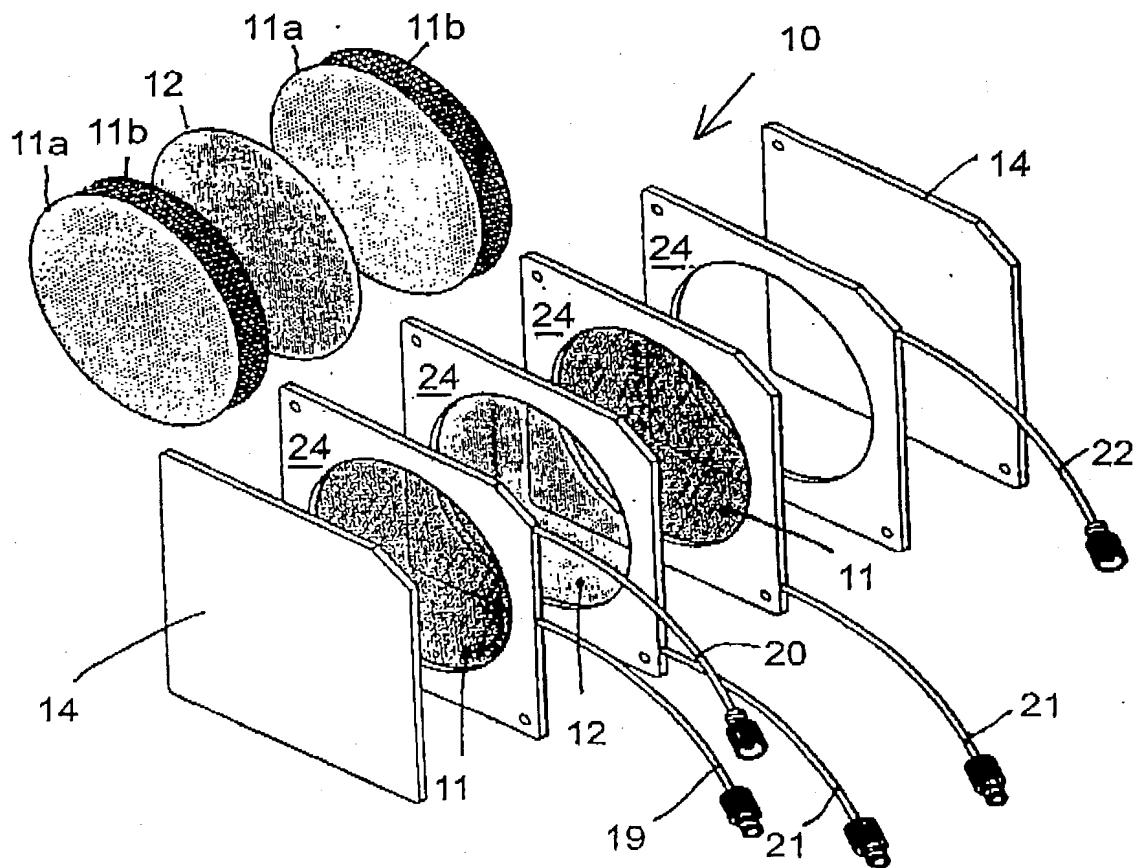
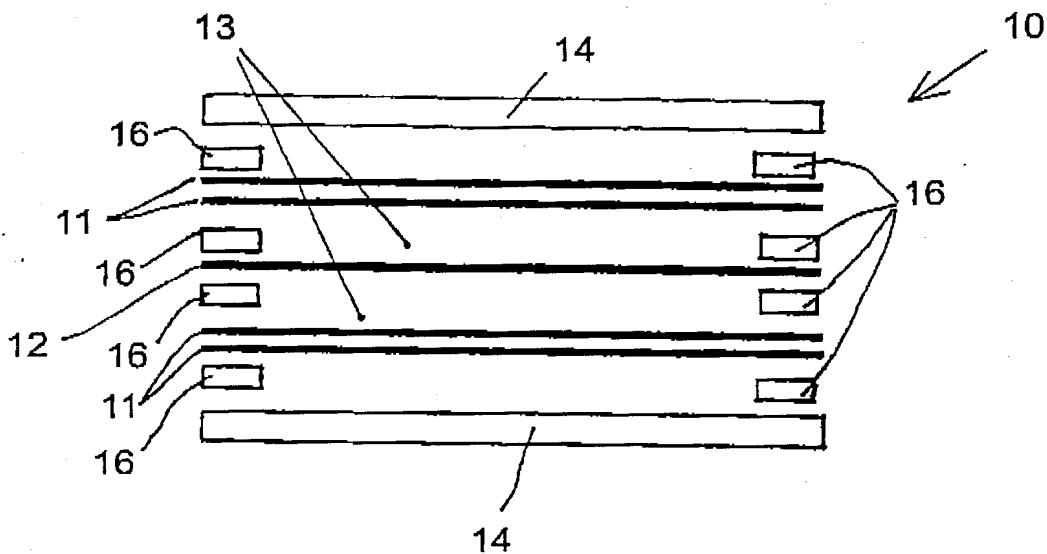


FIG. 2

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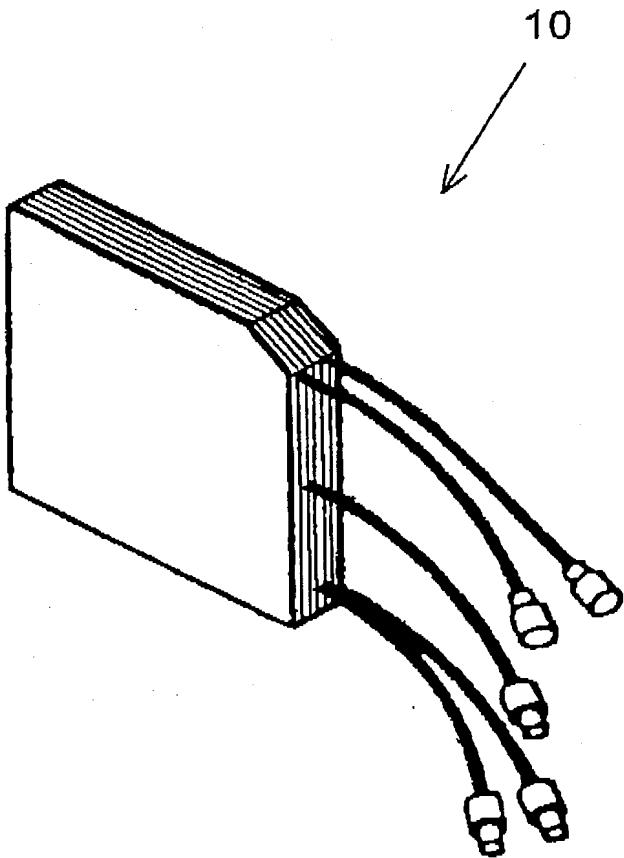
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FIG. 3



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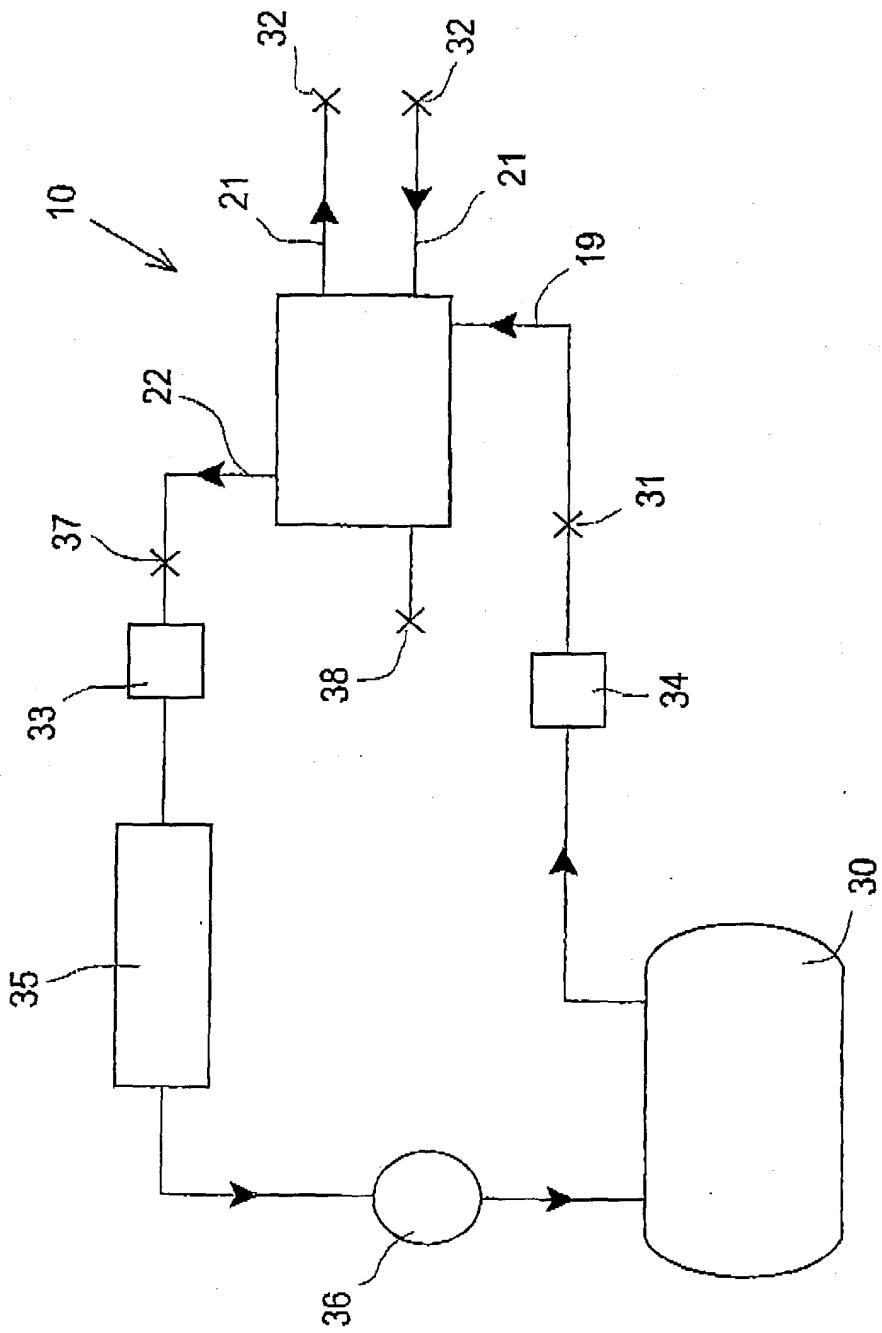
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FIG. 4

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Fig. 5

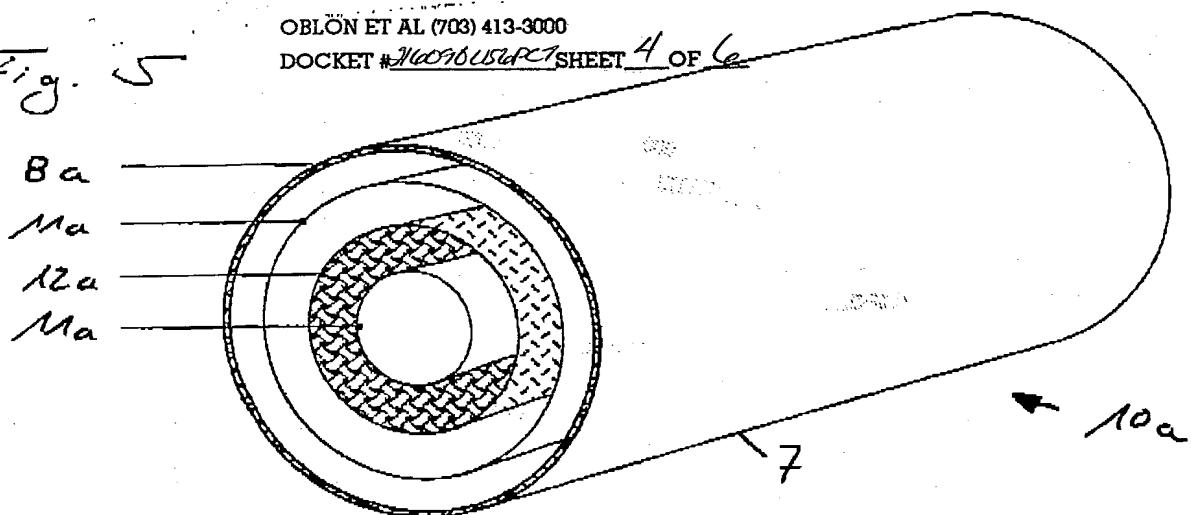


Fig. 6

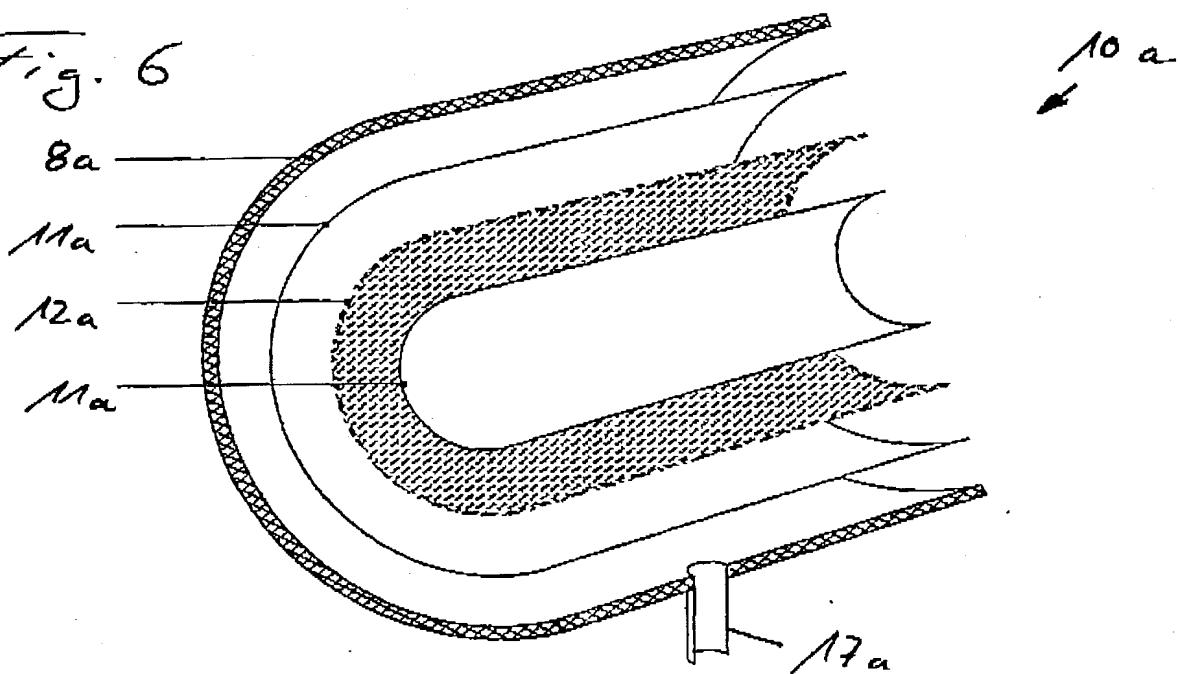
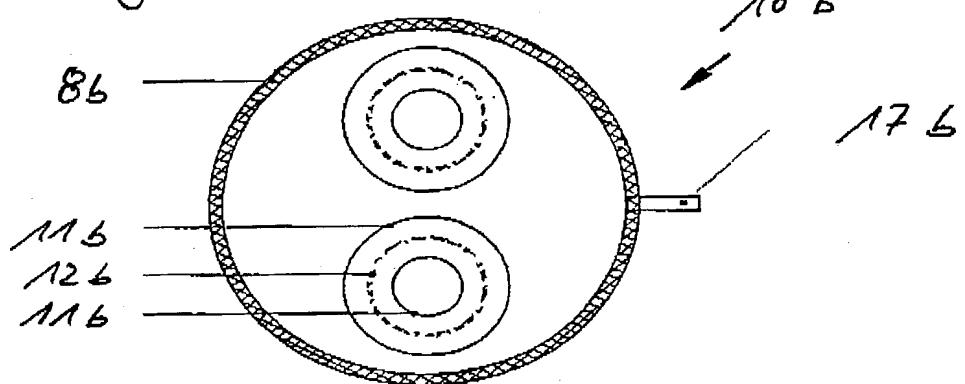


Fig. 7



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Fig. 8

10c →

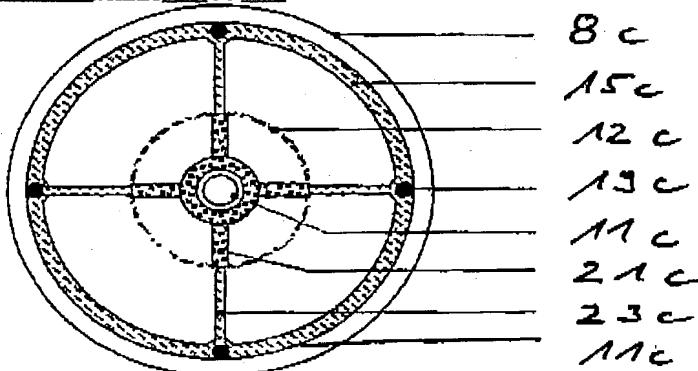


Fig. 9

10c →

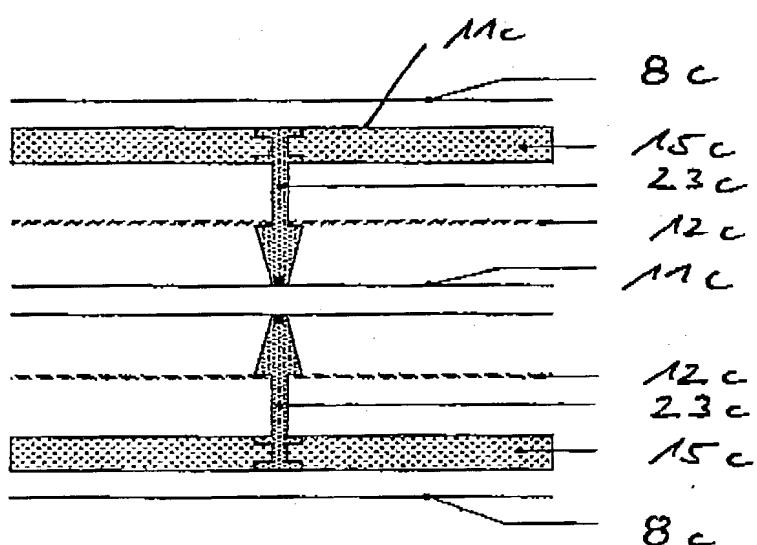
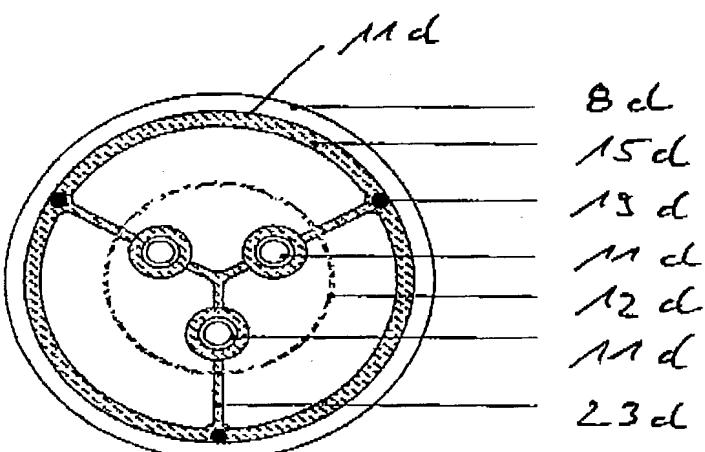


Fig. 10

10d →



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Fig. 11
10e →

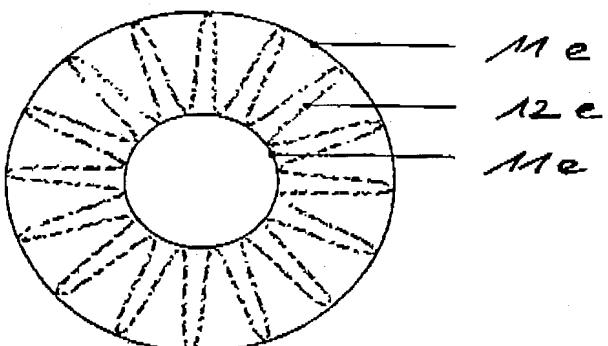


Fig. 12
10f →

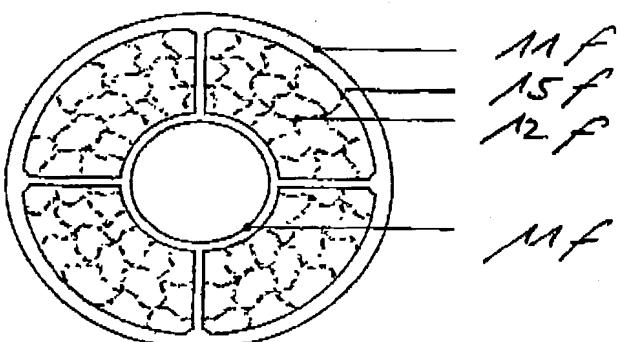


Fig. 13

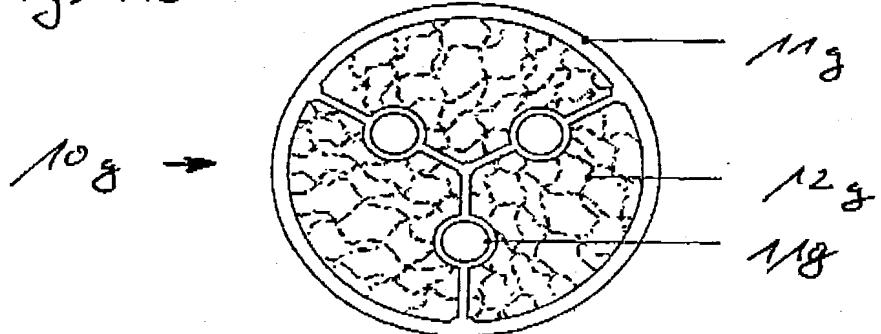
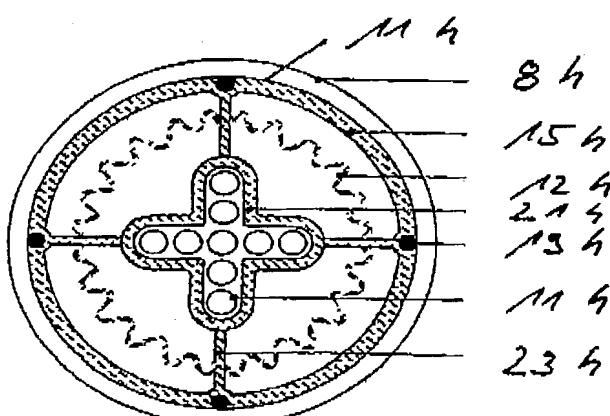


Fig. 14
10h →



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Declaration and Power of Attorney for Patent Application

Erklärung für Patentanmeldungen mit Vollmacht

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Bioreaktor

deren Beschreibung:

ist beigefügt
 wurde angemeldet am _____

unter der US-Anmeldenummer oder unter der Internationalen Anmeldenummer im Rahmen des Vertrags über die Zusammenarbeit auf dem Gebiet des Patentwesens (PCT)

_____ und am

_____ abgeändert (falls zutreffend).

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As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

Bioreactor

the specification of which:

is attached hereto.
 was filed on _____

as United States Application Number or PCT International Application Number

_____ and was amended on

_____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56.

German Language Declaration

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Prior foreign application(s)
(Frühere ausländische Anmeldungen)

199 32 439.5	Germany
(Number)	(Country)
(Nummer)	(Land)

I hereby claim foreign priority under Title 35, United States Code, § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT International application which designated at least one country other than the United States, listed below, and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed.

Priority claimed

Priorität beansprucht

12/07/1999	<input checked="" type="checkbox"/> Yes Ja	<input type="checkbox"/> No Nein
(Day/Month/Year Filed) (Tag/Monat/Jahr der Anmeldung)		
	<input type="checkbox"/> Yes Ja	<input type="checkbox"/> No Nein
(Day/Month/Year Filed) (Tag/Monat/Jahr der Anmeldung)		

Ich Beanspruche hiermit Prioritätsvorteile unter Title 35, US-Code, § 119(e) aller US-Hilfsanmeldungen wie unten aufgezählt.

(Application No.) (Aktenzeichen)	(Filing Date) (Anmeldetag)
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(Application No.) (Aktenzeichen)	(Filing Date) (Anmeldetag)
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(Application No.) (Aktenzeichen)	(Filing Date) (Anmeldetag)
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I hereby claim the benefit under Title 35, United States Code, § 120 of any United States application(s), or § 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application.

PCT/EP00/06355	July 5, 2000
(Application No.) (Aktenzeichen)	(Filing Date) (Anmeldetag)

(Status) (patented, pending, abandoned)
(Status) (patentiert, schwebend, aufgegeben)

(Application No.) (Aktenzeichen)	(Filing Date) (Anmeldetag)
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Ich erkläre hiermit, daß alle in der vorliegenden Erklärung von mir gemachten Angaben nach bestem Wissen und Gewissen der Wahrheit entsprechen, und ferner daß ich diese eidesstattliche Erklärung in Kenntnis dessen ablege, daß wissentlich und vorsätzlich falsche Angaben oder dergleichen gemäß § 1001, Title 18 des US-Code strafbar sind und mit Geldstrafe und/oder Gefängnis bestraft werden können und daß derartige wissentlich und vorsätzlich falsche Angaben die Rechtswirksamkeit der vorliegenden Patentanmeldung oder eines aufgrund deren erteilten Patentes gefährden können.

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(Status) (patentiert, schwebend, aufgegeben)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

German Language Declaration

VERTRETUNGSVOLLMACHT: Als benannter Erfinder beauftrage ich hiermit den (die) nachstehend aufgeführten Patentanwalt (Patentanwälte) und/oder Vertreter mit der Verfolgung der vorliegenden Patentanmeldung sowie mit der Abwicklung aller damit verbundenen Angelegenheiten vor dem US-Patent- und Markenamt: (Name(n) und Registrationsnummer(n) auflisten)

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith: (list name and registration number)



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German Language Declaration

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(Supply similar information and signature for third and subsequent joint inventors.)